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KILYK & BOWERSOX, P.L.L.C.
400 HOLIDAY COURT
SUITE 102
WARRENTON, VA 20186

EXAMINER

BARNHART, LORA ELIZABETH

ART UNIT	PAPER NUMBER
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1651

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/588,804	Applicant(s) NAKATSUJI ET AL.	
	Examiner Lora E. Barnhart	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 September 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 6-10 and 17-23 is/are pending in the application.
- 4a) Of the above claim(s) 10 and 19-21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 6-9, 17, 18, 22 and 23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 9/29/09 to claims 6 and 8 have been entered. Claims 1-5 and 11-16 have been canceled. Claims 22 and 23 have been added. Claims 6-10 and 17-23 remain pending in the current application, of which claims 6-9, 17, 18, 22, and 23 are being considered on their merits. Claims 10 and 19-21 remain withdrawn from consideration at this time. References not included with this Office action can be found in a prior action. Any rejections of record not particularly addressed below are withdrawn in light of the claim amendments and applicant's comments.

Election/Restrictions

Applicant's election without traverse of the species "collagen," "epithelial cell growth factor," and "fetal lung fibroblasts" in the reply filed on 3/30/09 is still in effect over the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 17, 18, and 23 are/remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9, 17, and 18 require that the cells in the method undergo division "twenty or more times on average." It is not clear whether the "average" refers to the number of divisions within a single culture vessel or to the number of divisions in numerous culture

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vessels over time. Applicant alleges that several kinds of cells may be present within a culture vessel, so the “average” refers to the “average” number of divisions for the several kinds of cells. See reply, page 6. These arguments have been fully considered, but they are not persuasive. It is submitted that applicant’s comments serve to further obfuscate the issue, since they add yet another interpretation to the claim language. The claims should stand on their own and fully, particularly, and distinctly describe the invention without any supplement from applicant’s remarks. Applicant must clarify this issue within the claims.

Claim 23 recites the limitation “epithelial cell growth factor,” which is queried. There is no molecule that the art unequivocally recognizes as “epithelial cell growth factor.” The examiner suspects applicant intended to recite “epidermal growth factor.” Clarification is required. If the claim is amended to include the term “epidermal growth factor,” applicant should point out the basis for this new limitation in the specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 6, 9, 17, 18, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto et al. (2002, U.S. Patent Application Publication 2002/0031828) taken in view of Goodheart (2004, U.S. Patent Application Publication 2004/0023322), Reich (1990, U.S. Patent 4,973,466; reference E), Benedict et al. (1992, U.S. Patent 5,108,923), and Wei et al. (2003, U.S. Patent Application Publication 2003/0017485).

Yamamoto teaches a method for culturing 3T3 mouse embryonic lung fibroblasts in a medium containing fetal bovine serum (FBS, which contains growth factors; paragraph 30). Yamamoto teaches that feeder layers may be yielded by sterilizing the fibroblasts by irradiation or addition of mitomycin C (paragraph 3).

Yamamoto does not teach a medium containing the claimed amounts of BSA and insulin and does not specifically suggest using the basal media listed in claim 1. Yamamoto does not specifically indicate how many divisions the 3T3 cells should undergo prior to being inactivated. Yamamoto does not teach all of the basal media recited in claim 6.

Goodheart teaches a medium for growing MRC-5 cells (human fetal lung fibroblasts) in Medium 199 supplemented with 10mg insulin/L of medium (paragraph

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59). Goodheart teaches that the amount of insulin in the media may vary and specifically contemplates varying the components in the media (paragraphs 59 and 60).

Reich teaches that insulin is a mitogen, i.e. that it promotes cell division (ccolumn 6, lines 1-8).

Benedict teaches that FBS contains BSA (column 9, lines 57-58). Benedict teaches that both BSA and FBS promote adhesion of mammalian cells to culture dishes (Table 4 at column 10). Benedict teaches that the amount of FBS (and, therefore, BSA) is optimizable based on the requirements of a given application (column 9, lines 52-54).

Wei teaches suitable culture media for mammalian cells (paragraph 58).

A person of ordinary skill in the art would have had a reasonable expectation of success in culturing the 3T3 mouse embryonic lung fibroblasts of Yamamoto to yield a feeder layer by culturing the cells in a medium comprising serum albumin, insulin, and Medium 199 because Goodheart teach that similar cells (human embryonic lung fibroblasts) can be cultivated in such a medium. Substituting the BSA of Goodheart for (or adding the BSA to) the FBS of Yamamoto would have constituted routine optimization, the skilled artisan recognizing that Benedict teaches that both of these agents promote cell adhesion. The skilled artisan would have been motivated to include insulin in the medium of Yamamoto because Reich teaches that insulin promotes proliferation.

Determining the amount of BSA and insulin to include in the medium of Yamamoto would have constituted routine optimization, since Benedict teaches that the amount of FBS (and, therefore, BSA) may be modified to suit downstream applications

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and since Reich teaches that insulin promotes cell proliferation. Because the goal of Yamamoto's method is to produce a confluent feeder layer adhered to a culture dish (paragraph 3, e.g.), determining the amount of BSA to promote adhesion, the amount of insulin to promote proliferation (and, therefore, formation of a continuous sheet), and the number of doublings to permit the cells to undergo would all have constituted routine optimization.

The selection of the basal mammalian culture media from the list in claim 1 would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Wei teaches that these media are functional equivalents for mammalian cell culture. A holding of obviousness over the cited claims is therefore clearly required.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute varying amounts of the BSA of Benedict for the FBS in the medium of Yamamoto or any of the media of Wei and to include the insulin of Goodheart and Reich in the medium of Yamamoto or any of the media of Wei because Goodheart suggests including these components in fetal lung fibroblast culture and because Benedict and Reich suggest optimizing the amounts of these components in mammalian cell culture.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto, Goodheart, Reich, Benedict, and Wei as applied to claims 6, 9, 17, 18, and 22 above, and further in view of Franzblau (1986, U.S. Patent 4,565,784; reference A).

The teachings of Yamamoto, Goodheart, Reich, Benedict, and Wei are relied upon as above. Yamamoto, Goodheart, Reich, Benedict, and Wei do not suggest culturing lung fibroblasts in vessel coated with an adhesion factor, e.g. collagen.

Franzblau teaches culturing lung fibroblasts on culture dishes coated with collagen (Example 2 at column 4, line 55). Franzblau teaches that lung fibroblasts cultured on collagen proliferate and grow more easily (column 5, lines 3-6).

A person of ordinary skill in the art would have had a reasonable expectation of success in culturing the 3T3 lung fibroblasts of Yamamoto in vessel coated with a cell adhesion factor, e.g. collagen, because Franzblau teaches that similar cells may be cultured on collagen-coated dishes. The skilled artisan would have been motivated to culture cells on dishes coated with a cell adhesion factor because Franzblau teaches that similar cells grow better on collagen (column 5, lines 3-6).

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto, Goodheart, Reich, Benedict, and Wei as applied to claims 6, 9, 17, 18, and 22 above, and further in view of Tang et al. (2004, U.S. Patent Application Publication

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2004/0059098). In the interest of compact prosecution, “epithelial cell growth factor” is interpreted as referring to “epidermal growth factor,” EGF.

The teachings of Yamamoto, Goodheart, Reich, Benedict, and Wei are relied upon as above. Yamamoto, Goodheart, Reich, Benedict, and Wei do not suggest including EGF in the media.

Tang teaches that EGF promotes proliferation of human lung fibroblasts (paragraphs 333 and 335).

A person of ordinary skill in the art would have had a reasonable expectation of success in including the EGF of Tang in the medium of Yamamoto in view of Goodheart, Reich, Benedict, and Wei because Tang teaches that mammalian lung fibroblasts may be cultured with EGF. The skilled artisan would have been motivated to include EGF because Tang teaches that this growth factor promotes proliferation of fibroblasts.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Response to Arguments

Regarding the obviousness rejections of record, applicant alleges that none of the references teaches culturing cells without serum. See reply, page 7, last paragraph continued to page 8. Applicant alleges that the Hook publication (previously cited) is not prior art in light of the submission of a certified translation of the foreign priority document. See reply, page 8. These arguments have been fully considered, but they are not persuasive.

The claims do not require that the medium used in the method be free of serum, only that it comprise serum albumin (which is a component of serum) and insulin as well as a defined medium such as Medium 199. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In any case, even if the claims were limited to methods comprising culturing in medium without serum, Goodheart's medium is serum-free, and Goodheart teaches the desirability of eliminating serum from the culture (see paragraph 61).

Regarding the teachings of Hook, the Franzblau reference is cited herein in place of Hook as teaching substantially similar concepts regarding the growth of lung fibroblasts on collagen-coated dishes. It is submitted that the Franzblau reference fully addresses the relevant claim elements.

This action is non-final to allow applicants a fair opportunity to reply; the disqualification of the Hook reference necessitated this action being made non-final. However, the examiner emphasizes that applicant's reply other than the perfection of the foreign priority claim was unpersuasive as to the substance of the obviousness rejection. Applicant has made no argument that the cited references are non-analogous and has submitted no evidence of unexpected results; a similar reply to this Office action is unlikely to establish that the claims are allowable and will almost certainly yield a final rejection.

In *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the Supreme Court reiterated the standard for overcoming obviousness rejections initially

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set forth in *Graham v. Deere*, namely convincing arguments that the cited art is non-analogous, a showing that the prior art teaches away from the claimed invention, or a showing of secondary considerations, e.g. truly unexpected results (see *KSR* at 1399). “When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103.” *Id.* at 1397. See also *In re Fout*, 675 F.2d 297, 301 (CCPA 1982) (“Express suggestion to substitute one equivalent for another need not be present to render such substitution obvious.”). In this case, the claimed method appears to be an obvious variant of the primary reference’s method; applicant has neither pointed to evidence in the specification as evidence of nonobviousness nor submitted declarations supported by evidence as a showing of patentability. A reply lacking such evidence is unlikely to overcome the pending obviousness rejections, given the direction of the Court in *KSR*. In the interest of compact prosecution, the examiner urges applicant to consider submitting objective evidence of truly unexpected results that are both practically and statistically significant. For example, applicants might show that the selection of a particular amount of one component is critical to a particular unexpected result and also amend the claims such that they are commensurate in scope with that showing.

No claims are allowed. No claims are free of the art.

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Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651